PCT/IL 99 / 00019

09/[illegible]

4

IL99/619

STATE PF ISRAEL

זאת לתעודה כי
רצופים בזה העתקים
נכונים של המסמכים
שהופקדו לכתחילה
עם הבקשה לפטנט
לפי הפרטים הרשומים
בעמוד הראשון של
הנספח.

This is to certify that annexed bereto is a true copy of the documents as originally deposited with the patent application particulars of which are specified on the first page of the annex.

היום 23 -11- 1999 This

ממונה על הבוחנים

רשם הפטנטים
Registrar of Patents

נתאשר
Certified

חוק הפטנטים, התשכ"ז -- 1967
PATENTS LAW, 5727-1967

בקשה לפטנט
Application for Patent

C:32029

לשימוש הלשכה
For Office Use

מספר Number	127129
תאריך: Date	18 -11- 1998
הוקדם/נדחה Ante/Post-dates	

אני, (שם המבקש, מענו -- ולגבי גוף מאוגד -- מקום התאגדותו)
I (Name and address of applicant, and, in case of body corporate-place of incorporation)

BIOSOMA LTD.
5 Safir Street
Ramat Gan

(An Israeli company)

ביוסומה בע"מ
רח' ספיר 5
רמת גן

חברה ישראלית

Inventor: Azariah Jossifoff
(An Israeli citizen)

הממציא: עזריה יוסיפוף
(אזרח ישראלי)

שמשמה הוא By Assignment
Owner, by virtue of

בעל אמצאה מכח העברה
of an invention, the title of which is:

(בעברית)
(Hebrew)
שיטה להכנת טבלית פרוגסרון לשמוש וגינאלי וטבליות שמוכנות כך

(באנגלית)
(English)
METHOD OF PREPARATION OF PROGESTERONE TABLET FOR VAGINAL DELIVERY AND TABLETS SO PREPARED

hereby apply for a patent to be granted to me in respect thereof
מבקש בזאת כי ינתן לי עליה פטנט

*בקשה חלוקה - Application for Division	*בקשת פטנט מוסף - Application for Patent of Addition	*דרישה דין קדימה Priority Claim		
מבקשת פטנט from Application	*לבקשה/לפטנט to Patent/Appl.	מספר/סימן Number/Mark	תאריך Date	מדינת האיגוד Convention Country
No._____ מס._____	No._____ מס._____			
dated_____ מיום	dated_____ מיום			
*יפוי כח: כללי/מיוחד - רצוף בזה / עוד יוגש P.O.A.: general / individual - attached / to be filed later -				
filed in case_____ הוגש בענין				
המען למסירת הודעות ומסמכים בישראל Address for Service in Israel Sanford T. Colb & Co. P.O.B. 2273 Rehovot 76122				
חתימת המבקש Signature of Applicant For the Applicant, Sanford T. Colb & Co. C:32029		היום 17 בחודש NOVEMBER שנת 1998 This of the year		

לשימוש הלשכה
For Office Use

טופס זה, כשהוא מוטבע בחותם לשכת הפטנטים ומושלם בספר ובתאריך ההגשה, הינו אישור להגשת הבקשה שפרטיה רשומים לעיל.
This form, impressed with the Seal of the Patent Office and indicating the number and date of filing, certifies the filing of the application, the particulars of which are set out above.

* מחק את המיותר Delete whatever is inapplicable

שיטה להכנת טבלית פרוגסרון לשמוש וגינאלי וטבליות שמוכנות כך

METHOD OF PREPARATION OF PROGESTERONE TABLET FOR VAGINAL DELIVERY AND TABLETS SO PREPARED

BIOSOMA LTD.

ביוסומה בע"מ

Inventor: Azariah Jossifoff

הממציא: עזריה יוסיפוף

C:32029

METHOD OF PREPARATION OF PROGESTERONE TABLET FOR VAGINAL DELIVERY AND TABLETS SO PREPARED

Field of the Invention

The invention relates to the preparation of pharmaceutical compositions containing progesterone, in particular to compositions for vaginal delivery of progesterone.

Background of the Invention

Since its discovery in the 1950's, synthetic oral progesterone has been used for a variety of gynecological conditions. However, androgenic activity inherent in the synthetic compound precludes its liberal use in assisted reproductive technology (ART) because of the threat of teratogenic effects.

Furthermore, synthetic progesterone used in hormonal replacement therapy (HRT) may partially reverse the estrogenic benefits on the cardiovascular system and lipoprotein metabolism (Lobo, Am. J. Obstet. Gynecol. **166** (1992), 1997-2004; Fahraeus et al., Eur. J. Clin. Invest. **13** (1983), 447-453; Ottosson et al., Am. J. Obstet. Gynecol. **151** (1985), 746-750; Knopp, Am. J. Obstet. Gynecol. **158** (1988), 1630-1643; Crook et al., **166** (1992) 950-954).

Natural progesterone is devoid of any androgenic activity that might compromise lipoprotein metabolism or induce teratogenicity. Moreover, it probably has a direct beneficial effect on blood vessels (Jiang et al., Eur. J. Pharmacol. **211** (1992), 163-167).

The major difficulty in utilizing natural progesterone is its route of administration. Oral intake is hampered by rapid and extensive intestinal and liver metabolism, leading to poorly sustained serum levels and low bioavailability (Adlercreutz et al., J. Steroid Biochem. **13** (1980), 231-244; Arafat et al., Am. J. Obstet. Gynecol. **159** (1988), 1203-1209; Whitehead et al., Brit. Med. J. **280** (1980), 825-827; Ottosson et al., Br. J. Obstet. Gynecol. **91** (1984), 1111-1119; Padwick et al., Fertil. Steril. **46** (1986), 402-407; Nahoul et al., Maturitas **16** (1993), 185-202; Nillus et al., Am. J. Obstet. Gynecol. **110** (1971), 470-477; Chakmakjian et al., J.

Reprod. Med. 32 (1987), 443-448). Intramuscular injection assures reliable absorption, but is painful, can cause local irritation and cold abscesses (Devroey et al., Int. J. Fertil. 34 (1989), 188-193), must be administered by trained medical personnel, and often suffers from low patient compliance.

For these reasons, the vaginal route has become the most established way in which to deliver natural progesterone. The progesterone is easily administered to the vagina, which has a large potential of absorption, and also avoids liver first-pass metabolism when delivered to the vagina.

Many vaginal formulations have been assayed, mostly as suppositories (Price et al., Fertil. Steril. 39 (1983), 490-493; Norman et al., Fertil. Steril. 56 (1991), 1034-1039; Archer et al., Am. J. Obstet. Gynecol., 173 (1995), 471-478), gelatin capsules (Devroey et al., Int. J. Fertil. 34 (1989), 188-193; Smitz et al., Hum. Reprod. 2 (1992), 309-314; Miles et al., Fertil. Steril. 62 (1994), 485-490), and recently as bio-adhesive gels (Fanchin et al., Obstet. Gynecol. 90 (1997), 396-401; Ross et al., Am. J. Obstet. Gynecol. 177 (1997), 937-941).

Although the suppositories are easily inserted, they melt at body temperature and lead to disturbing vaginal discharge. Oral gelatin capsule containing micronized progesterone have also been used vaginally (Devroey et al., Int. J. Fertil. 34 (1989), 188-193; Smitz et al., Hum. Reprod. 2 (1992), 309-314; Miles et al., Fertil. Steril. 62 (1994), 485-490), but insertion of a small capsule high into the vagina is difficult and large doses of 600 to 800 mg are needed to achieve adequate plasma concentration (Smitz et al., Hum. Reprod. 2 (1992), 309-314; Miles et al., Fertil. Steril. 62 (1994), 485-490; Bourgain et al., Hum. Reprod. 5 (1990), 537-543).

U.S. Patent No. 5,084,277 to Greco et al. discloses a process for the preparation of a progesterone-containing tablet.

Summary of the Invention

The present invention seeks to provide a method for the production of a tablet for the vaginal delivery of progesterone.

There is thus provided, in accordance with a preferred embodiment of the invention, a method for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor.

There is also provided, in accordance with another preferred embodiment of the invention, a method for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor, including an effervescent; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor, including an effervescent.

There is further provided, in accordance with another preferred embodiment of the invention, a method for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone does not exceed the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

sieving a first lubricant to obtain a sieved first lubricant;

mixing said substantially dry micronized progesterone with said sieved first lubricant and a material selected from a first filler or a disintegrant to form a first mixture;

mixing a binder which binds dry particles with said first mixture to form a second mixture;

intimately mixing an effervescent and a first quantity of a second filler to form a third mixture;

sieving said third mixture to obtain a sieved third mixture, and then intimately mixing said sieved third mixture and said second mixture to form a fourth mixture;

intimately mixing the fourth mixture with a second quantity of said second filler to form a fifth mixture;

sieving a second lubricant and a material selected from a saponificant or a third lubricant to obtain, respectively, sieved second lubricant and sieved third lubricant;

intimately mixing said sieved second lubricant and said sieved third lubricant with said fifth mixture to form a sixth mixture; and

tabletting said sixth mixture by direction compaction to form a tablet.

In a preferred embodiment of the invention, the amount of water mixed with the micronized progesterone is between about 25 and 28 wt.% of the amount of micronized progesterone.

In another preferred embodiment of the invention, the water is added to the micronized progesterone at rate of between about 6-9 ml per minute, at a mixing speed of between about 25-33.3 rpm.

In another preferred embodiment of the invention, the first lubricant is sieved through sieves having a pore size of between about 400 and 450 microns, preferably about 425 microns.

In another preferred embodiment of the invention, the third mixture is sieved through sieves having a pore size of between about 400 and 450 microns, preferably about 425 microns prior to mixing with the second mixture.

In another preferred embodiment of the invention, said sieved second lubricant and said sieved third lubricant are sieved through sieves having a pore size of between about 100 and 150 microns, preferably 125 microns prior to mixing with said fifth mixture.

In one preferred embodiment of the invention, said drying of said wetted micronized progesterone is done at a temperature of between about 55°C and about 60°C.

In another preferred embodiment of the invention, all of said mixing steps are carried out at a temperature of between about 15°C and 30°C.

In one preferred embodiment of the invention, said first lubricant is silicon dioxide (colloidal anhydrous silica).

In another preferred embodiment of the invention, said material selected from a first filler or a disintegrant is a starch exhibiting good flow properties, such as

cornstarch 1500 or other starches derived from corn (maize), potatoes or wheat, as are well known in the art.

In a preferred embodiment of the invention, the binder which binds dry particles is polyvinylpyrrolidone (povidone), e.g. Povidone 30.

In another preferred embodiment of the invention, said second filler is derived from a natural source and is more preferably lactose or is composed principally of lactose (e.g. ludipress, which as is well known in the art is a commercially available mixture of polyvinylpyrrolidone and lactose).

In a preferred embodiment of the invention, said effervescent is a mixture of a pharmaceutically acceptable carboxylic or dicarboxylic acid, such as adipic acid or tartaric acid, and a pharmaceutically acceptable salt of HCO_3^-, such as sodium bicarbonate. Preferably the acid and bicarbonate are present in an amount providing a molar excess of -COOH groups.

In another preferred embodiment of the invention, said first portion and said second portion of said second filler are of generally the same size.

In one preferred embodiment of the invention, the effervescent is prepared prior to said intimate mixing of said first portion of said second filler with said effervescent. In another preferred embodiment of the invention, said effervescent is prepared *in situ* as part of said intimate mixing of said first portion of said second filler with said effervescent.

In a preferred embodiment of the invention, said intimate mixing of said first portion of said second filler with said effervescent comprises non-intimately mixing said first portion of said second filler with said effervescent and passing the resultant non-intimately mixed mixture through a sieve having an average pore size between

about 400 and 450 microns, preferably about 425 microns diameter to obtain said third mixture.

In a preferred embodiment of the invention, the effervescent comprises between about 6 and 10 wt.%, preferably about 8 wt.% of the tablet.

In one preferred embodiment of the invention, said intimate mixing of said second mixture with said third mixture to obtain said fourth mixture is accomplished by non-intimately mixing said second mixture with said third mixture to obtain a non-intimately mixed mixture and sifting said non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns, preferably about 425 microns diameter to obtain said fourth mixture.

In a preferred embodiment of the invention, said second lubricant is selected from magnesium stearate, talc, sodium lauryl sulfate, and phosphates known in the art to function as lubricants.

In another preferred embodiment of the invention, said material selected from a saponificant or a third lubricant is sodium lauryl sulfate.

There is also provided in accordance with another preferred embodiment of the invention a tablet prepared by the steps of: slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone; drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone; mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor; and forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor.

There is also provided in accordance with another preferred embodiment of the invention a tablet prepared by the steps of: slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone; drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone; mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor, including an effervescent; and forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor, including an effervescent.

There is also provided in accordance with another preferred embodiment of the invention a tablet prepared by the steps of: slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone; drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone; sieving a first lubricant to obtain a sieved first lubricant; mixing said substantially dry micronized progesterone with said sieved first lubricant and a material selected from a first filler or a disintegrant to form a first mixture; mixing a binder which binds dry particles with said first mixture to form a second mixture; intimately mixing an effervescent and a first quantity of a second filler to form a third mixture; sieving said third mixture to obtain a sieved third mixture, and then intimately mixing said sieved third mixture and said second mixture to form a fourth mixture; intimately mixing the fourth mixture with a second quantity of said second filler to form a fifth mixture; sieving a second lubricant and a material selected from a saponificant or a third lubricant to obtain, respectively, sieved second lubricant and sieved third lubricant; intimately mixing said sieved second lubricant

and said sieved third lubricant with said fifth mixture to form a sixth mixture; and tabletting said sixth mixture by direction compaction to form a tablet.

Detailed Description of the Preferred Embodiments

The invention will be better understood through the following illustrative and non-limitative description and examples of preferred embodiments of the invention.

Example 1

Preparation of Tablets

Step 1: To 1000 g of micronized progesterone were added 280 g of distilled water, with mixing using a planetary mixer, over a period of 30 minutes. After mixing, the wetted micronized progesterone was spread on pans to thickness of about 4-5 mm, and the pans then placed in an oven at 58°C. The humidity was checked periodically using a humidity checker. When the humidity of the micronized progesterone was reduced to substantially 0%, the dried micronized progesterone was either used immediately in step 2 as described below, or was stored in dry, sealed containers for later use in step 2.

Step 2: Colloidal anhydrous silica (Aerosil 380, 25 g) was sieved through a Russel sieve having pores of 425 micron size, and mixed for 10 minutes with 1000 g of micronized progesterone from Step 1 and 2100 g of maize 1500 starch, using an Angelsman mixer at 32 RPM, to form Mixture A. At the end of the 10 minutes of mixing, 490 g of povidone 30 were added to Mixture A, and mixing was continued for another ten minutes, to prepare "Mixture B".

Step 3: Lactose (Ludipress, BASF, 3800 g), adipic acid (570 g) and sodium bicarbonate (430 g) were mixed for 10 minutes at room temperature using an Angelsman mixer at 32 RPM. Following mixing, these ingredients were sieved through a Russel sieve having pores of 425 microns to obtain "Mixture C".

Step 4: Mixtures B and C were mixed for 10 minutes at room temperature using an Angelsman mixer at 32 RPM to obtain "Mixture D".

Step 5: Mixture D (4800 g) was mixed with 3800 g of lactose (Ludipress) for 10 minutes at room temperature using an Angelsman mixer at 32 RPM, to obtain "Mixture E".

Step 6: Magnesium stearate (230 g) and sodium lauryl sulfate (50 g) were sieved through a Russel sieve (pore size 125 microns). The sieved magnesium stearate and sodium lauryl sulfate were then mixed for with mixture E for 20 minutes at room temperature using an Angelsman mixer, to obtain "Mixture F".

Step 7: Tablets were obtained from mixture F by direct compaction using an Eko Korsch Press. The amounts of ingredients listed in this example are suitable for production of 10,000 tablets each containing about 100 mg progesterone.

Example 2

Using the above process, tablets of 1187 mg to 1312 mg total weight, containing from 90 to 110 mg progesterone, were obtained.

Example 3

The process described in Example 1 was modified by doubling the amount of filler (Ludipress) to obtain tablets containing on average 50 mg progesterone.

Example 4

The pharmacokinetics and clinical use of tablets prepared in accordance with the invention were evaluated as follows: 50 healthy, post-menopausal women with intact uteri, 39 of whom had suffered premature menopause and 11 who were truly postmenopausal, all of whom were undergoing hormone replacement therapy (HRT), submitted blood samples for determination of baseline profiles of hormones (progesterone and other hormones) and other biochemicals (bilirubin, cholesterol,

etc.). The blood samples were taken at 8 AM on the first day of the evaluation (day 0) in a fasting state, by intravenous indwelling catheter which was introduced into the cubital vein. Non-estrogen primed postmenopausal women were chosen in order to avoid confusion with endogenous progesterone secretion and estrogen influence on vaginal mucosa absorption (Villanueva et al., Fertil. Steril. 35 (1981), 433-437).

The women then self-administered the progesterone vaginal tablet using a plastic applicator and lay down for 20 minutes. Repeat blood samples for progesterone concentration were withdrawn 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours after the vaginal insertion. Blood was allowed to clot at room temperature for 1 hour, after which the serum was separated by centrifugation and stored at -20°C until analysis.

To evaluate clinical use of the drug, the women were instructed to insert tablets prepared in accordance with the present invention, containing the same dose as administered on day 0, twice daily starting on day 1, and to recline for 20 minutes after each insertion. On days 14 and 30, blood samples for comparison with the baseline were drawn in the morning while the subjects were in a fasting state.

Of the 50 women who participated in the evaluation, 20 were allocated tablets containing 50 mg progesterone, and the remainder of the participants received tablets containing 100 mg progesterone. The baseline details of the participants are summarized in Table I.

Table I

	Tablets containing 50 mg progesterone	Tablets containing 100 mg progesterone	Total
Median age (years)	43 ± 6.1	43.2 ± 7.9	43.3 ± 7.2
Age range (years)	28-53	28-55	28-55
Height (cm)	161.3 ± 8.6	161.6 ± 5.7	161.5 ± 6.9
Weight (kg)	67.1 ± 11.5	62.8 ± 13.1	64.5 ± 12.5
BMI (kg/m^2)	25.9 ± 4.2	24.0 ± 4.4	24.8 ± 4.4

Data are expressed as mean ± standard deviation unless otherwise specified. Body mass index (BMI) was calculated as weight in kg divided by the square of height in meters.

A single vaginal application of a 50 mg progesterone-containing tablet prepared in accordance with the invention resulted in the rapid increase of plasma progesterone concentration. The mean peak plasma level (T_{max}), mean elimination half-life ($T_{1/2}$), maximal serum concentration (C_{max}), and AUC (area under the curve, i.e. total amount of plasma progesterone observed) derived from the blood samples taken on day 0 of the evaluation are summarized in Table II.

Table II

	Progesterone dose	
	50 mg (20 subjects)	100 mg (30 subjects)
T_{max} (hours)	6.1 ± 2.63	6.4 ± 3.35
$T_{1/2}$ (hours)	13.18 ± 1.3	13.7 ± 1.05
C_{max} (nmol/liter)	20.43 ± 8.01	31.61 ± 12.62[a]
AUC (nmol/hour/liter)	154.15 ± 60.31	247.61 ± 123.04[b]

Values are mean ± standard deviation; [a]P = 0.0004; [b]P = 0.001.

As shown in Table III, after 14 and 30 days of continuous application twice daily, the serum P levels were significantly higher compared to baseline values on day 0. No statistically significant difference in plasma levels of follicle stimulating hormone, leutinizing hormone, estradiol, cortisol, dehydroepiendosterone sulfate, or aldosterone were observed in the study groups between baseline values and after continued administration of the tablets of the invention. Similarly, the plasma levels of serum glutamic oxaloacetic transaminase, alkaline phosphatase, cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, and very low density lipoprotein did not change significantly between the baseline measurement and the measurements at 14 and 30 days of twice-daily administration.

Table III

Blood Progesterone levels, nmol/liter

Day sample was taken	Progesterone dose	
	50 mg (20 subjects)	100 mg (30 subjects)
Day 0[a]	1.05 ± 0.7	3.0 ± 2.4
Day 14[a]	17.48 ± 9.8[b]	26.08 ± 13.96[b]
Day 30[a]	17.38 ± 14.39	21.42 ± 16.32

[a]P = 0.0001, significant difference between progesterone baseline values on day 0 compared to day 14 and day 30; [b]P = 0.02.

It will be appreciated that various features of the invention which are, for clarity, described in the contexts of separate embodiments may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment may also be provided separately or in any suitable subcombination.

It will also be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather the scope of the invention is defined only by the claims which follow:

CLAIMS

1. A method for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor.

2. A method according to claim 1 for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor, including an effervescent; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor, including said effervescent.

3. A method according to claim 2 for preparing a tablet for the vaginal administration of progesterone for systemic use, comprising the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone does not exceed the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

sieving a first lubricant to obtain a sieved first lubricant;

mixing said substantially dry micronized progesterone with said sieved first lubricant and a material selected from a first filler or a disintegrant to form a first mixture;

mixing a binder which binds dry particles with said first mixture to form a second mixture;

intimately mixing an effervescent and a first quantity of a second filler to form a third mixture;

sieving said third mixture to obtain a sieved third mixture, and then intimately mixing said sieved third mixture and said second mixture to form a fourth mixture;

intimately mixing said fourth mixture with a second quantity of said second filler to form a fifth mixture;

sieving a second lubricant and a material selected from a saponificant or a third lubricant to obtain, respectively, sieved second lubricant and sieved third lubricant;

intimately mixing said sieved second lubricant and said sieved third lubricant with said fifth mixture to form a sixth mixture; and

tabletting said sixth mixture by direction compaction to form a tablet.

4. A method according to claim 3, wherein said first lubricant is sieved through sieves having a pore size of between about 400 and 450 microns.

5. A method according to claim 4, wherein said first lubricant is sieved through sieves having a pore size of about 425 microns.

6. A method according to any of claims 3 to 5, wherein said third mixture is sieved through sieves having a pore size of between about 400 and 450 microns

7. A method according to claim 6, where said pore size is about 425 microns.

8. A method according to any of claims 3 to 7 wherein said sieved second lubricant and said sieved third lubricant are sieved through sieves having a pore size of between about 100 and 150 microns.

9. A method according to claim 8, wherein said pore size is about 125 microns.

10. A method according to any of claims 3 to 9, wherein said first lubricant is silicon dioxide (colloidal anhydrous silica).

11. A method according to any of claims 3 to 10, wherein said material selected from a first filler or a disintegrant is a starch exhibiting good flow properties.

12. A method according to claim 11 wherein said starch is derived from corn (maize), potatoes or wheat.

13. A method according to claim 12 wherein said starch is cornstarch 1500.

14. A method according to any of claims 3 to 13, wherein said binder which binds dry particles is polyvinylpyrrolidone (povidone).

15. A method according to claim 14, wherein said binder which binds dry particles is Povidone 30.

16. A method according to any of claims 3 to 15, wherein said second filler is derived from a natural source.

17. A method according to claim 16, wherein said second filler is selected from lactose or a composition composed principally of lactose.

18. A method according to any of claims 3 to 17, wherein said first portion and said second portion of said second filler are of generally the same size.

19. A method according to any of claims 3 to 18, wherein said effervescent is prepared prior to said intimate mixing of said first portion of said second filler with said effervescent.

20. A method according to any of claims 3 to 18, wherein said effervescent is prepared *in situ* as part of said intimate mixing of said first portion of said second filler with said effervescent.

21. A method according to any of claims 3 to 20, wherein said intimate mixing of said first portion of said second filler with said effervescent comprises non-intimately mixing said first portion of said second filler with said effervescent and passing the resultant non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns, to obtain said third mixture.

22. A method according to claim 21, wherein said intimate mixing of said first portion of said second filler with said effervescent comprises non-intimately mixing said first portion of said second filler with said effervescent and passing the resultant non-intimately mixed mixture through a sieve having an average pore size of about 425 microns diameter to obtain said third mixture.

23. A method according to any of claims 3 to 22, wherein said intimate mixing of said second mixture with said third mixture to obtain said fourth mixture is

accomplished by non-intimately mixing said second mixture with said third mixture to obtain a non-intimately mixed mixture and sifting said non-intimately mixed mixture through a sieve having an average pore size between about 400 and 450 microns to obtain said fourth mixture.

24. A method according to claim 23, wherein said intimate mixing of said second mixture with said third mixture to obtain said fourth mixture is accomplished by non-intimately mixing said second mixture with said third mixture to obtain a non-intimately mixed mixture and sifting said non-intimately mixed mixture through a sieve having an average pore size of about 425 microns diameter to obtain said fourth mixture.

25. A method according to any of claims 3 to 24, wherein said second lubricant is selected from magnesium stearate, talc, sodium lauryl sulfate, and phosphates known in the art to function as lubricants.

26. A method according to claim 25, wherein said lubricant is magnesium stearate.

27. A method according to any of claims 3 to 26, wherein said material selected from a saponificant or a third lubricant is sodium lauryl sulfate.

28. A method according to any of claims 2 to 27, wherein said effervescent is a mixture of a pharmaceutically acceptable carboxylic or dicarboxylic acid and a pharmaceutically acceptable salt of HCO_3^-.

29. A method according to claim 28, wherein said pharmaceutically acceptable carboxylic or dicarboxylic acid is selected from adipic acid or tartaric acid.

30. A method according to claim 28 or 29, wherein said pharmaceutically acceptable salt of HCO_3^- is as sodium bicarbonate.

31. A method according to any of claims 28 to 30, wherein said pharmaceutically acceptable carboxylic or dicarboxylic acid and said bicarbonate are present in an amount providing a molar excess of -COOH groups.

32. A method according to any of claims 28 to 31, wherein said effervescent comprises a mixture of adipic acid and sodium bicarbonate.

33. A method according to any of claims 2-32, wherein said effervescent comprises between about 6 and 10 wt.%, preferably about 8 wt.% of the tablet.

34. A method according to any of claims 1 to 33 wherein the amount of water mixed with said micronized progesterone is between about 25 and 28 wt.% of the amount of micronized progesterone.

35. A method according to claim 34, wherein the amount of water mixed with said micronized progesterone is about 28 wt.% of the amount of micronized progesterone.

36. A method according to any of claims 1 to 35, wherein said water is added to said micronized progesterone at rate of between about 6 to 9 ml per minute.

37. A method according to any of claims 1 to 36, wherein said water is mixed with said micronized progesterone at a mixing speed of between about 25-33.3 rpm.

38. A method according to any of claims 1 to 37 wherein said drying of said wetted micronized progesterone is done at a temperature of between about 55°C and about 60°C.

39. A method according to any of claims 1 to 38 wherein all of said mixing steps are carried out at a temperature of between about 15°C and 30°C.

40. A tablet prepared by the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor.

41. A tablet prepared by the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone not exceeding the maximum wetting capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

mixing said substantially dry micronized progesterone with other pharmaceutically acceptable excipients or diluents therefor, including an effervescent; and

forming a tablet by direct compaction of said substantially dry micronized progesterone which has been mixed with said other pharmaceutically acceptable excipients or diluents therefor, including said effervescent.

42. A tablet prepared by the steps of:

slowly mixing water with micronized progesterone, the total amount of water mixed with said micronized progesterone does not exceed the maximum wetting

capacity of the amount of micronized progesterone, whereby to obtain wetted micronized progesterone;

drying said wetted micronized progesterone to a humidity content of substantially 0%, whereby to form substantially dry micronized progesterone;

sieving a first lubricant to obtain a sieved first lubricant;

mixing said substantially dry micronized progesterone with said sieved first lubricant and a material selected from a first filler or a disintegrant to form a first mixture;

mixing a binder which binds dry particles with said first mixture to form a second mixture;

intimately mixing an effervescent and a first quantity of a second filler to form a third mixture;

sieving said third mixture to obtain a sieved third mixture, and then intimately mixing said sieved third mixture and said second mixture to form a fourth mixture;

intimately mixing said fourth mixture with a second quantity of said second filler to form a fifth mixture;

sieving a second lubricant and a material selected from a saponificant or a third lubricant to obtain, respectively, sieved second lubricant and sieved third lubricant;

intimately mixing said sieved second lubricant and said sieved third lubricant with said fifth mixture to form a sixth mixture; and

tabletting said sixth mixture by direction compaction to form a tablet.

43. A method according to any one of claims 1-39, substantially as hereinbefore described.

44. A tablet according to any one of claims 40-42, substantially as hereinbefore described.

For the Applicant:

Sanford T. Colb & Co.
C:32029